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PRAZOSIN DOES NOT ALTER CANINE RENIN RELEASE IN RESPONSE TO SYSTEMIC HYPOTENSION OR INTRARENAL ISOPRENALINE AND PROSTAGLANDIN I_2 INFUSION

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1 The effect of a hypotensive dose of intravenous prazosin (0.2 mg/kg) on heart rate and plasma renin activity was evaluated in anaesthetized mongrel dogs pretreated with indomethacin.

2 The effect of prazosin on the renin release elicited by the β-adrenoceptor agonist isoprenaline and by prostaglandin I_2 was also evaluated.

3 Prazosin administration was associated with a significant increase in heart rate and increase in plasma renin activity.

4 Prazosin did not interfere with the increase in plasma renin activity in response to either isoprenaline or prostaglandin I_2.

5 We conclude that prazosin is not a unique peripheral vasodilator since hypotensive doses are associated with an increase in heart rate and plasma renin activity. In addition, prazosin does not inhibit the release of renin induced by either isoprenaline or prostaglandin I_2.

Introduction

Prazosin is an antihypertensive agent that acts primarily on peripheral arterioles to block post-synaptic α-adrenoceptors (Wood, Phelan & Simpson, 1975; Graham, Oates, Stoker & Stokes, 1977; Cambridge, Davey & Massingham, 1977). Prazosin is reported to differ from other directly acting vasodilators by producing a reduction of arterial pressure without invoking a reflex tachycardia and renin release (Massingham & Hayden, 1975; Graham, Muir & Hayes, 1976; Wood, Bolli & Simpson, 1976). The purpose of this study was to elucidate the mechanism of the presumed inhibition of renin release by determining the effect of prazosin on the renin release elicited by the β-adrenoceptor agonist, isoprenaline and by prostaglandin I_2 (PGI_2).

Methods

Animal preparation

A total of seven mongrel dogs weighing 18 to 35 kg were anaesthetized with sodium pentobarbitone (30 mg/kg i.v.) and supplemented as needed to maintain surgical anaesthesia. After endotracheal intubation, the dogs were ventilated with room air by means of a constant volume respirator. The right femoral artery was cannulated for the continuous recording of blood pressure and heart rate, and the right femoral vein was cannulated for the administration of drugs. The right kidney in each dog was exposed through a flank incision and functionally removed by ligating and severing the renal artery, vein and nerves. The left kidney was exposed through a flank incision and denervated by cutting the renal nerves and swabbing the artery with a 5% phenol solution. A non-cannulating electromagnetic flow probe was placed around the left renal artery for continuous monitoring of renal blood flow, and a 25 gauge needle was placed in the renal artery for infusion of isoprenaline or PGI_2. The left renal vein was cannulated for blood collection for the determination of plasma renin activity, and the left ureter was cannulated for collection of urine.

Experimental design

Indomethacin (8 mg/kg i.v.) was administered 20 min before the start of the experiment to inhibit prostaglandin synthesis. Half way through the experiment and 40 min before the administration of prazosin, indomethacin (4 mg/kg i.v.), was administered to supplement the previous dose. Each experiment was divided into 4 parts. During parts 1 and 2 the responses to isoprenaline and PGI_2 were determined

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and during parts 3 and 4 the effects of prazosin on the responses to isoprenaline and PGI_2 were observed. The responses measured were urinary sodium excretion rate, mean arterial pressure, heart rate, renal blood flow and renal venous plasma renin activity. Each part consisted of a 10 min baseline period followed by 10 min intrarenal infusions of two doses of isoprenaline ($0.01\ \mu g\ kg^{-1}\ min^{-1}$ and $0.03\ \mu g\ kg^{-1}\ min^{-1}$) or PGI_2 ($3\ ng\ kg^{-1}\ min^{-1}$ and $10\ ng\ kg^{-1}\ min^{-1}$). In each part only one drug was infused, and the drugs were randomized so that some dogs received isoprenaline during part 1 and others received PGI_2. The experimental parts were separated by 1 h to allow the responses to return to baseline values before the experiment was continued. One hour after the end of part 2, baseline values for urinary sodium excretion rate, mean arterial pressure, heart rate, renal blood flow and renal venous plasma renin activity were determined. Following these measurements, prazosin (0.2 mg/kg i.v. bolus) was administered and when mean arterial pressure had stabilized (20 min) new baseline values for the various parameters were determined as previously described and the 3rd part was begun. Parts 3 and 4 were identical in design to parts 1 and 2, therefore the results from parts 3 and 4 determined the effects of isoprenaline and PGI_2 on the various parameters in the presence of prazosin. After part 4 was completed, sodium arachidonate was infused intrarenally ($10\ \mu g\ kg^{-1}\ min^{-1}$) and changes in renal blood flow were recorded. The sodium arachidonate infusion was used to determine whether prostaglandin synthesis was indeed inhibited by indomethacin.

Following cannulation of the ureter, a solution of 0.9% w/v NaCl solution (saline) was given intravenously at a constant rate to replace the fluid volume excreted by the kidneys. Plasma renin activity was determined on 5 ml of blood collected into precooled vials containing 0.2 ml of 10% ethylenediaminetetraacetate (EDTA) by the technique of Stockigt, Collins & Biglieri (1971). Urine sodium concentration was determined by flame photometry.

(−)-Isoprenaline bitartrate (Isoproterenol bitartrate, Sigma, St. Louis) was dissolved in saline. Prostaglandin I_2 (Upjohn, Kalamazoo, MI) was dissolved in 0.9% $NaHCO_3$ and adjusted to pH 8.8 with sodium carbonate. Sodium arachidonate was prepared in arachidonic acid (Nu-Check, Elysian, MN) and sodium carbonate buffer (pH 8.5) to make the sodium salt of the fatty acid.

Mean comparisons for the effect of prazosin on mean arterial pressure, heart rate, renal blood flow and plasma renin activity immediately before and 20 min after prazosin (Table 1) were made by a paired t test. Mean comparisons to baseline values for mean arterial pressure, heart rate, renal blood flow and urinary sodium excretion rate before and after prazosin (Table 2) were made by randomized complete block design and then Dunnett's procedure. Mean comparisons for plasma renin activity to isoprenaline and prostaglandin I_2 in the presence and absence of prazosin (Figure 1) was made using multiple t test comparisons correcting for the new alpha.

Results

Table 1 shows mean arterial pressure and heart rate immediately before and 20 min after prazosin (0.2 mg/kg i.v. bolus). Prazosin administration significantly reduced mean arterial pressure from 134 ± 9 mmHg ($\bar{x} \pm$ s.e. mean) to 110 ± 8 mmHg ($P < 0.05$). Concomitant with the reduction in mean arterial pressure was a significant ($P < 0.05$) increase in heart rate from 151 ± 10 beats/min ($\bar{x} \pm$ s.e. mean) to 175 ± 9 beats/min ($\bar{x} \pm$ s.e. mean). Prazosin did not change renal blood flow but significantly ($P < 0.05$) increased renal vein plasma renin activity 132% from 2.01 ± 0.40 ng angiotensin I $ml^{-1}\ h^{-1}$ to 4.66 ± 1.10 ng angiotensin I $ml^{-1}\ h^{-1}$ (Table 1).

Table 2 shows that the intrarenal infusion of the high dose of PGI_2 produced a small but statistically significant reduction in mean arterial pressure before and after prazosin. Isoprenaline at both the low and

Table 1 Effect of prazosin (0.2 mg/kg) on systemic and regional haemodynamics and plasma renin activity

	Before prazosin	*After prazosin*
Mean arterial pressure (mmHg)	134 ± 9	110 ± 8*
Heart rate (beats/min)	151 ± 10	175 ± 9*
Renal blood flow (ml/min)	218 ± 39	227 ± 36
Plasma renin activity (angiotensin I ng $ml^{-1}\ h^{-1}$)	2.01 ± 0.40	4.67 ± 1.10*

Each value is the mean of 7 experiments and is shown with the standard error. *$P < 0.05$.

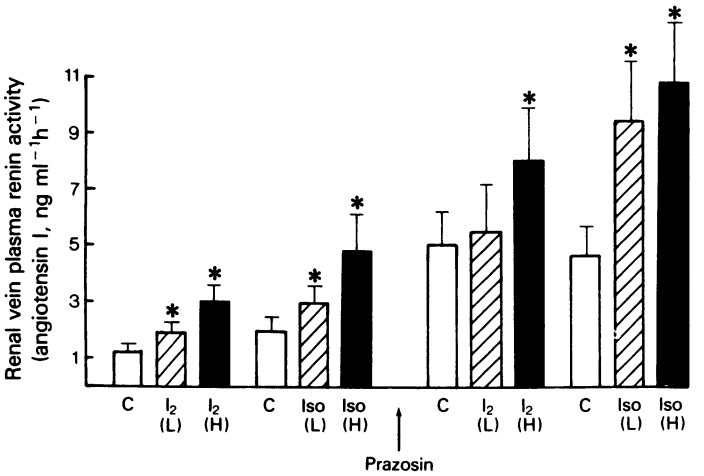

Figure 1 Effect of intrarenal prostaglandin I_2 at 3 ng kg^{-1} min^{-1} (I_2 (L)) and 10 ng kg^{-1} min^{-1} (I_2 (H)) and isoprenaline at 0.01 μg kg^{-1} min^{-1} (Iso (L)) and 0.03 μg kg^{-1} min^{-1} (Iso (H)) on plasma renin activity (angiotensin I, ng ml^{-1} h^{-1}). C = baseline or control value. Prostaglandin I_2 and isoprenaline significantly increased from baseline values plasma renin activity in the absence and presence of prazosin (0.2 mg/kg i.v. bolus). Columns represent mean values of 7 experiments. Vertical lines indicate standard errors. *$P < 0.05$.

high intrarenal infusion rates produced a small but significant reduction in mean arterial pressure before prazosin. Following prazosin, isoprenaline did not alter mean arterial pressure at either intrarenal infusion rate. Heart rate response to PGI_2 did not change significantly before and after prazosin. Only isoprenaline at the high dose had any significant effect on heart rate and only when administered in the absence of prazosin. Table 2 also shows that both PGI_2 and isoprenaline significantly increased renal blood flow at both doses and prazosin did not alter these responses. Urinary sodium excretion rate was not changed by either isoprenaline or PGI_2 in the absence or presence of prazosin (Table 2).

The intrarenal infusion of PGI_2 and isoprenaline significantly elevated renal vein plasma renin activity (Figure 1). Prazosin did not interfere with either the β-adrenoceptor-mediated or the prostaglandin-

Table 2 Effect of intrarenal isoprenaline and prostaglandin I_2 on systemic and regional haemodynamic parameters and urinary sodium excretion in the absence and presence of prazosin

Parameter	*Intervention*	B	(L) Iso	(H) Iso	B	(L) PGI_2	(H) PGI_2
MAP	Control	142 ± 6	139 ± 6*	137 ± 6*	143 ± 7	140 ± 8	134 ± 9*
	Prazosin	104 ± 9	102 ± 8	103 ± 7	106 ± 8	104 ± 9	100 ± 8*
HR	Control	133 ± 8	144 ± 10	155 ± 12*	128 ± 13	128 ± 11	132 ± 12
	Prazosin	159 ± 13	163 ± 12	158 ± 11	162 ± 7	159 ± 6	153 ± 5
RBF	Control	231 ± 30	250 ± 32*	260 ± 34*	205 ± 30	245 ± 38*	284 ± 45*
	Prazosin	212 ± 39	246 ± 41*	259 ± 42*	227 ± 39	250 ± 42*	280 ± 46*
^{U}Na	Control	32 ± 17	39 ± 18	39 ± 17	50 ± 31	53 ± 27	61 ± 26
	Prazosin	13 ± 5	12 ± 5	12 ± 4	12 ± 4	12 ± 4	14 ± 5

Each value is the mean of 7 experiments and is shown with the standard error. MAP = mean arterial pressure (mmHg); HR = heart rate (beats/min); RBF = renal blood flow (ml/min); ^{U}Na = urinary sodium excretion rate; B = baseline values; (L)Iso = isoprenaline 0.01 μg kg^{-1} min^{-1} intra-renal infusion (μEq/min); (H)Iso = isoprenaline 0.03 μg kg^{-1} min^{-1} intra-renal infusion; (L)PGI_2 = prostaglandin I_2 3 ng kg^{-1} min^{-1} intrarenal infusion; (H)PGI_2 = prostaglandin I_2 10 ng kg^{-1} min^{-1} intrarenal infusion. *$P < 0.05$.

mediated increase in plasma renin activity. Although prazosin administration alone significantly increased baseline plasma renin activity, both isoprenaline and PGI_2 were able to stimulate renin release above this baseline value.

Halfway through the experiment and 40 min before the administration of prazosin, indomethacin (4 mg/kg i.v.) was given to supplement the previous dose. The indomethacin supplementation did not change plasma renin activity or renal blood flow from the previous basal values. Basal plasma renin activity before supplementation with indomethacin was 1.8 ± 0.5 ng angiotensin I $ml^{-1} h^{-1}$. Thirty minutes after indomethacin the value was 2.0 ± 0.4 ng angiotensin I $ml^{-1} h^{-1}$. Basal renal blood flow was 224 ± 37 ml/min and 30 min after the supplementation with indomethacin, renal blood flow was 218 ± 39 ml/min.

At the end of each experiment, the vasodilatation observed with intrarenal arachidonic acid ($10 \mu g\, kg^{-1}\, min^{-1}$) infusion was totally blocked indicating that renal cortical prostaglandin synthesis was inhibited (Gerber, Data & Nies, 1978).

Discussion

Antihypertensive agents including hydralazine, diazoxide, sodium nitroprusside and minoxidil stimulate renin release and elicit a reflex sympathetically-mediated increase in heart rate (Kuchel, Fishman, Liddle & Michelakis, 1967; Kaneko, Ikeda, Takeda & Ueda, 1967; Pettinger, Campbell & Keeton, 1973). Prazosin has been reported to be a novel antihypertensive drug devoid of the acute reflex tachycardia and renin release (Massingham & Hayden, 1975; Graham *et al.*, 1976; Wood *et al.*, 1976). However, our findings do not substantiate this claim.

The intravenous administration of prazosin in anaesthetized dogs pretreated with indomethacin reduced mean arterial pressure and increased heart rate and renal vein plasma renin activity (Table 1). We have previously shown that the macula densa and baroreceptor mechanisms of renin release require endogenous prostaglandin production (Data, Gerber, Crump, Frölich, Hollifield & Nies, 1978; Olson, Skoglund, Nies & Gerber, 1979). In the present study, the macula densa and baroreceptor mechanisms of renin release were inactivated by inhibiting prostaglandin synthetase with indomethacin. In addition, the kidney was denervated. Thus, the increase in plasma renin activity elicited by prazosin was most probably due to a reflex release of catecholamines from the adrenal medulla acting on β-adrenoceptors.

Prazosin did not have any direct effects on the juxtaglomerular apparatus to inhibit or attenuate the release of renin by β-adrenoceptor or prostaglandin mediated mechanisms (Figure 1). Thus, prazosin does not interfere with the ability of the kidney to respond to either endogenous or exogenous stimuli for renin release.

Our observations contradict several other reports. Graham *et al.*, 1976 found that prazosin (0.1 mg/kg i.v. bolus) acutely depressed plasma renin activity in normotensive dogs. Similarly, Wood & Lee (1974) described a significant fall in plasma renin activity by day four in genetically hypertensive rats given prazosin, 25 mg/kg, daily. Massingham & Hayden (1975) found that prazosin (0.1 mg/kg i.v.) in conscious renal hypertensive dogs produced no significant acute change in heart rate or plasma renin activity. However, their data for plasma renin activity before and 2 h after prazosin administration showed that prazosin in fact significantly increased plasma renin activity ($P < 0.05$) if reanalyzed with a paired t test. In contrast to the above results and in agreement with our data, Fernandes, Smith, Weder, Kim, Gould, Busby, Swartz & Onesti (1975) found a significant increase in peripheral plasma renin activity by 430 to 470% to prazosin (1 mg/kg i.v.) in normotensive Wistar rats. In addition, Rubin & Blaschke (1979) recently reported that the hypotension produced by prazosin in normal human volunteers was associated with an unopposed rise in plasma renin activity and heart rate.

In view of our experimental findings, prazosin does not appear to be unique as a peripheral vasodilator since a reflex release of renin and a tachycardia are associated with its administration.

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